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PhRMA

1155 June 3, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 01N-0322; Institutional Review Boards; Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews; Advance Notice of Proposed Rulemaking; 67 *Federal Register* 10115, March 6, 2002

Dear Sir/Madam:

The following comments on the above Advanced Notice of Proposed Rulemaking (ANPR) are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over $30 billion in the discovery and development of new medicines.

General

PhRMA does not believe that the proposed regulation warrants introduction. If sponsors, IRBs and clinical investigators are in compliance with the current system and regulations there is no need for additional rulemaking in regard to so-called "IRB shopping". Neither FDA nor the Office of the Inspector General (OIG) has demonstrated through factual evidence that a problem exists relative to "IRB shopping." Rulemaking in this area should not be considered until persuasive data is available from a representative sampling of IRBs in the United States. The OIG recommended regulatory action on the strength of having "heard of (only) a few situations" of "IRB shopping", and the recommendation was justified in terms of an assumed principle of good practice. Indeed, recent high profile cases of problems involving failures of protection for research participants have not involved "IRB shopping".

The dearth of any such experiences or factual evidence indicates that the call for this regulatory action would only add a significant regulatory burden for sponsors, investigators and IRBs and not support the public health. The requisites of the proposed requirements themselves indicate an enormous amount of activity would be generated for sponsors, clinical investigators and IRBs. The result would be unwarranted cost, time delays and possible interruption to patient treatment. Instead of

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the proposed regulation, FDA inspections and IRB accreditation is the better approach to address the overall concerns raised by the OIG report.

The notice suggests a number of possible steps for the future (e.g., all prior IRB reviews could be disclosed to IRBs to explain their reasons for approving a study). These comments in the notice are open ended, unfocused, and do not have a specific end in mind. To PhRMA's knowledge, there is no evidence in the OIG report or from other sources to suggest, let alone prove, that such changes in regulations will yield measurable improvements in the protection of human subjects. Any changes in the regulations in 21 CFR Parts 56 and 312 must be based on specific and detailed evidence that the changes will yield measurable improvements in the protection of human subjects.

Response to Questions

1. How significant is the problem of IRB shopping?

Based on experience, "IRB shopping" as described in the document ("sponsors and/or research investigators who were unhappy with one IRB's review switched to another without the new IRB being aware of the other's prior involvement") occurs very infrequently and not in the manner intimated in the document. Instead, the very infrequent cases where a second IRB is asked to approve a study are a result of administrative rather than ethical issues. For example, it has been observed that the initial IRB requests a central (commercial) IRB be used because of excessive workload, lack of technical expertise or restrictions imposed by a regulatory agency. The initial IRB may not understand the protocol or has requested unnecessary and sometimes legally perilous additions to the protocol or informed consent form. Generally, if the IRB has concerns regarding the trial, the issues are either negotiated with change to the protocol, or if the institution does not finally approve, the trial is often times not placed at that center by the sponsor. In situations where a site is affiliated with an institution, the "institutional" IRB must allow a waiver of the review to the other IRB. At no time should a private-institution investigator seek central IRB approval unless the local IRB has granted a written waiver.

To characterize these infrequent experiences as "shopping" generates a negative and inaccurate connotation that fails to recognize that the switching to another IRB is aimed at redressing inadequacies with the initial IRB. Problems with the initial IRB include administrative issues unrelated to human subject protection (e.g., excessive workload) that could hamper the development of pharmaceutical products, as well as expertise deficiencies that could ultimately compromise patient safety. It is not the case that frequent replacement of IRBs is occurring. Rather, in the rare instance in which review by a second IRB is sought, the aim is to eliminate roadblocks to the development of pharmaceutical products unrelated to human subject protection. There certainly may be

exceptions, but for the vast majority of instances, the reasons are legitimate and do not affect human subject protection.

2. Who should make these disclosures?

Disclosure to IRBs about any prior IRB reviews should not be required. This suggestion, i.e., to have all prior reviews communicated to all IRBs, creates an enormous burden on the system without adding protection to human subjects. In actuality, an IRB should be able to make the correct decision concerning the study without any other information relative to decisions from other IRBs (with the exception of the case where a local IRB waives its review to a second IRB [21 CFR Part 56.114]). This independent assessment is the premise upon which the IRB process is based. In addition, modern clinical research entails a constant, asynchronous exchange of protocols and protocol amendments between sponsors and investigators and the IRBs reviewing them. Multicenter studies may have more than 100 sites, but the protocol is usually not reviewed concurrently at all of the sites. Moreover, many studies enlist sites in other countries as well as the United States (US), and foreign sites are likely to be bound by different regulations and to have different ethical review standards from American IRBs. A requirement to inform IRBs of all prior and pending reviews and the rationale for the IRB's approval or rejection would likely result in an IRB delaying its decision on the protocol until other IRB reviews have been conducted. This delay would allow the IRB to be thorough in considering all possible information, and thereby avoid being perceived as deficient or, even worse, as negligent. However, the delay could also impede efforts to get lifesaving drugs to patients as quickly as practicable. Mandatory disclosure would also impose an unreasonable burden on sponsor, investigators, and IRBs that would detract from conducting the trial rather than enhance subject safety.

Another problem with requiring disclosure of prior IRB reviews is that it creates the potential to introduce significant bias and "group think". Currently, IRB members may independently request opinions and information from any experts that they wish to consult. This informal information exchange and discussion engages the IRB members in an active decision-making process. As IRBs become dependent upon other IRBs, it is likely that the biases of certain IRBs would modify the human subject protection aspects of the study. Therefore, all opinions, positive and negative, from the US as well as from other countries globally would need to be included. Depending on the details of the study, this could be a massive amount of paperwork. This could also result in a "group think" phenomenon in that a particular perspective (and at worst a detrimental perspective) could dominate the study approval and review process

Another issue cited in the proposed rulemaking involved sponsors seeking IRB review. It should be noted that initial and ongoing communication with the IRB is the responsibility of the investigator under current FDA regulations. These proposed regulations recognize that the only situation in which the sponsor communicates directly with the IRBs is when an IND is withdrawn because of a safety reason (21 CFR

312.38). Therefore it should be made clear that the regulatory responsibility for seeking IRB review primarily belongs to the investigator.

3. Who should receive the disclosures?

This again is addressed in the above responses. An IRB should not need to learn of the decisions of another IRB if the first IRB is fulfilling its obligations properly. The requirement to inform other IRBs will complicate the approval and continuing review processes significantly while making no improvement to human subject protection. The only reasonable condition requiring a new regulation or change to an existing regulation would be to require the party seeking IRB approval to disclose to an IRB if a study protocol has been reviewed or disapproved by another IRB for the same research site. (Again it should be noted that from experience, this happens very infrequently and that disclosure of study disapproval for the research site is already interpreted by FDA as part of current regulation: 21 CFR Part 56.109 (a)[1].) In any other scenario the complexity of clinical research would render quite overwhelming the logistics of trying to ensure that each IRB was informed about the refusal or criticism of each protocol by all the other IRBs or ethics committees that had reviewed it. The additional administrative burden of trying to accomplish this would be completely disproportionate to any putative reduction in risk to study participants. In fact, it may actually increase risk if IRBs (already overburdened) are inundated with unnecessary information or if study activities are interrupted until it evaluates information from other IRBs.

4. What information should be disclosed?

All prior IRB reviews should not be disclosed. This would be an enormous administrative burden. There would be literally thousands of decisions that an IRB would need to consider. The burden to sponsors and investigators would also be immense. There is no deficiency in the currently established procedure that should make such disclosure necessary. Moreover, the information could be misinterpreted, breach confidentiality laws and be prejudicial. If all IRB decisions will need to be communicated, this would result in a never-ending stream of notifications across IRBs, investigators, and sponsors.

5. If a proposal would not require disclosure of all prior IRB decisions, what information should be disclosed?

This issue raises again the presupposition that the existing process does not provide for adequate review. By regulation (21 CFR part 56.111), an IRB needs to be able to consider the proposed research. These regulations require the IRB to be able to evaluate the research on its own (provided it is given the requisite documentation and

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[1] FDA Information Sheets; "Guidance for Institutional Review Boards and Clinical Investigators"; 1998; Frequently Asked Questions, #26.

information from the investigator). Dependencies on other reviews without explanation or context could prove to be detrimental to the evaluation of the research, and will certainly incur more cost and generate more bureaucracy than benefit. The only reasonable exception would be to require an investigator to indicate to the IRB whether he or she submitted the protocol to another IRB previously and whether it was disapproved for that site. The IRB then could determine if additional information was necessary.

6. To permit a subsequent IRB to assess the value of a prior IRB decision, should information about the basis for the prior decision be disclosed?

The previous comments address this question. The increased administrative burden and consequential potential for liability will make the research process perilously slow-moving without adding anything to human subject protection. In addition, the proposal to disclose information about the composition and expertise of the prior IRB membership will be impractical for a sponsor to obtain and summarize in any meaningful way for subsequent IRB review consideration. Again, this would be extremely burdensome and would require investigators and sponsors to obtain information to which they do not presently have ready access. Existing regulations require each individual IRB to be sufficiently constituted to independently assess proposed investigations.

7. How should FDA enforce the requirement?

Enforcement of this regulation, if it is enacted, should follow the current approach for other areas of human subject protection, which would be to evaluate it when Bioresearch Monitoring Program inspections are conducted. For example, during an inspection of a clinical investigator, the FDA investigator would review whether the regulations were followed. To implement a system of reporting to FDA failures to disclose seems to be an unreasonable burden, especially for FDA.

8. Are there other ways to deal with IRB shopping other than disclosure of prior IRB reviews?

The problem is not significant enough to warrant a new federal regulation. The only reasonable exception would be to require an investigator to indicate to the IRB whether he or she submitted the protocol to another IRB previously and whether it was disapproved for that site. The IRB then could determine if additional information was necessary. Most IRBs function well and ensure that ethical standards are met. For those few that may not meet current regulatory requirements, the FDA should use existing enforcement measures to secure appropriate and adequate operation.

Finally, FDA should not consider unilateral action on matters involving protection of human subjects. As FDA is well aware, the core Health and Human Services (HHS) regulations on protection of human subjects become the basis of a common federal policy since 1991. HHS and 16 other federal agencies adhere to this policy, known as the "Common Rule," thereby providing consistency in protection of human subjects, and reinforcing a common standard to enhance compliance among IRBs, investigators, sponsors, and institutions. The benefits of the Common Rule are substantial and should weigh against a proposed unilateral change by FDA or another Federal agency.

PhRMA trusts that these comments are useful to the FDA.

Sincerely,

Allan Goldhammer